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EXAMINER
STEADMAN, DAVID J

ART UNIT	PAPER NUMBER
1652	11

DATE MAILED: 03/27/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/720,096	NILSSON ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *18-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17 and 24-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Application Status

Claims 1-27 are pending in the application.

Applicants election with traverse of Group I, claims 1-17 and and 24-27, drawn to a method of modifying a substrate material by a bacterial culture that is active in said substrate and is not susceptible to attack by bacteriophage in Paper No. 9, filed 01/07/02 is acknowledged.

The examiner requests that applicants provide a copy of all pending claims in subsequent communications.

Lack of Unity

1. Applicants traverse the lack of unity on the grounds that the reference of Richardson (J Dairy Sci 66:2278-86) does not teach the claimed invention of Group I and therefore, the claims of Groups I and II relate to a single general inventive concept under PCT Rule 13.1. In view of applicants' arguments and upon further review of the cited reference, the examiner agrees that Richardson does not teach or suggest the methods of Group I as set forth in claims 1-3, 8-11, and 26. However, the modified lactic acid bacterium of claims 18 and 19 of Group II were known in the prior art (see for example Johansen *Dev Biol Stand* 85:531-34 and Dickely *Mol Microbiol* 15:839-847), Johansen and Dickely disclose purine auxotrophic strains, e.g., DN209, of Lactococcus lactis as encompassed by claims 18 and 19. While Johansen and Dickely do not teach that said auxotrophic strains are resistant to lysis by bacteriophage, the strains would inherently exhibit this characteristic as being purine auxotrophs. Thus, the bacteria of Group II do not constitute a special technical feature as defined by PCT Rule 13.2.

Claims 18-23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Claims 1-17 and 24-27 are examined on the merits.

Specification/Informalities

14. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: "Method of Preventing Bacteriophage Infection Using Auxotrophic Lactic Acid Bacteria". See MPEP § 606.01.
15. The specification is objected to because there is no "Brief Description of the Drawings" section. See MPEP § 608.01(f).
16. The sequence listing has been entered into the database with modification. Non-ASCII "garbage" has been deleted at the end of the file.
17. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows: An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78).

If applicant desires priority under 35 U.S.C. 119(e) based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph.

Claim Objections

18. Claims 24 and 25 are objected to as being dependent upon non-elected claims.
19. Claim 27 is objected to because of the following informalities: the term "that a lactic acid bacterial starter culture is infected by bacteriophages" is grammatically incorrect and should be replaced with, for example, "lactic acid bacterial starter culture infection by bacteriophages". Appropriate correction is required.

Claim Rejections - 35 USC § 101

2. Claim 26 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a

claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

20. Claims 1-17, 26, and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
21. Claim 1 (claims 2-17, 26, and 27 dependent therefrom) is unclear in the recitation of "attack by bacteriophages". The definition of the term has not been provided in the specification or the claims and the meaning of the term "attack by bacteriophages" is unclear. It is suggested that applicants clarify the meaning of the term by, for example, replacing the term with "cell lysis by bacteriophages".
22. Claims 4 and 5 are indefinite in the recitation of "including". It is unclear as to whether the method is practiced using any Pur- or thyA mutants or only with the specifically recited strains. It is suggested that applicants clarify the meaning of the claim.
23. Claim 26 is unclear in the recitation of "dairy flavour". It is suggested that, for example, applicants replace the term "dairy flavour" with "dairy flavouring".
24. Claim 26 provides for the use of a culture, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

25. Claims 1-17 and 24-27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1 (claims 9-11, dependent therefrom), 2-8, 12-17, and 24-27 are rejected because the claims recite a method of modifying a genus of substrate materials or a method of manufacturing a genus of food or feed products using a genus of modified lactic acid bacterium as follows: lactic acid bacteria with a genus of modifications; lactic acid bacteria with a genus of mutations that renders the strain auxotrophic and requiring a genus of compounds which are required for replication but are not present in the substrate, to disrupt DNA replication, RNA transcription, or protein synthesis in a genus of substrate materials which are limited with respect to a genus of compounds required for DNA replication, RNA transcription, or protein synthesis, said modified strains capable of carrying out a genus of metabolic reactions in said substrate, whereby the strain is not susceptible to attack or infection by bacteriophage; lactic acid bacteria with a genus of genetic modifications that result in an enhanced metabolic pathway, enhanced glycolytic flux, or enhanced flux throught the pentose phosphate pathway, enhanced ATPase activity; a genus of lactic acid bacteria mutants that do not perform DNA replication, RNA transcription, or protein synthesis under a genus of conditions, pH conditions, temperature conditions, composition of the substrate conditions and presence/absence of an inducer conditions; or a genus of lactic acid bacteria that are capable of increasing cell size without mitosis as encompassed by the claims. The specification teaches only a single representative species of such substrates as encompassed by the claims, i.e., milk, two representative species of such bacteria as encompassed by the claims, i.e., purine or thymidine

auxotrophic lactic acid bacterium, a single representative species of genetic modifications as encompassed by the claims, i.e., overexpression of F1-ATPase. Moreover, the specification fails to describe any other representative species of substrates, bacteria, or modifications by any identifying characteristics or properties other than being a substrate material, a food or feed product, a modified lactic acid bacterium as follows: lactic acid bacteria with a modification; lactic acid bacteria with a mutation that renders the strain auxotrophic and requiring a compound which is required for replication but is not present in the substrate, to disrupt DNA replication, RNA transcription, or protein synthesis in a substrate material which is limited with respect to a compound required for DNA replication, RNA transcription, or protein synthesis, said modified strains capable of carrying out a metabolic reaction in said substrate, whereby the strain is not susceptible to attack by bacteriophage; lactic acid bacteria with a genetic modification that results in an enhanced metabolic pathway, enhanced glycolytic flux, or enhanced flux throught the pentose phosphate pathway, enhanced ATPase activity; a lactic acid bacteria mutant that does not perform DNA replication, RNA transcription, or protein synthesis under a condition, pH condition, temperature condition, composition of the substrate condition and presence/absence of an inducer condition; or a lactic acid bacteria that is capable of increasing cell size without mitosis. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

26. Claims 1-17 and 24-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of acidifying milk by: a) propagating a starter culture of purine or thymidine auxotrophic lactic acid bacterium capable of acidifying milk in a medium containing purines or thymidine, respectively; and b) adding the starter culture to milk under conditions that allow acidification of the milk by the bacterium, whereby if the milk is contaminated with bacteriophage, the bacterium maintain the ability to acidify the milk, and optionally wherein the auxotrophic lactic acid bacteria overexpress F1-ATPase for increased carbon flux through the glycolytic pathway, does not reasonably provide enablement for a method of modifying *any* substrate material or a method of

manufacturing *any* food or feed product using *all* modified lactic acid bacterium as follows: lactic acid bacteria with *any* modification; lactic acid bacteria with *any* mutation that renders the strain auxotrophic and requiring a compound which is required for replication but is not present in the substrate, to disrupt DNA replication, RNA transcription, or protein synthesis in *any* substrate material which is limited with respect to *any* compound required for DNA replication, RNA transcription, or protein synthesis, said modified strain capable of carrying out *any* metabolic reactions in said substrate, whereby the strain is not susceptible to attack by bacteriophage; lactic acid bacteria with *any* genetic modifications that result in an enhanced metabolic pathway, enhanced glycolytic flux, or enhanced flux throught the pentose phosphate pathway, enhanced ATPase activity; *any* lactic acid bacteria mutants that does not perform DNA replication, RNA transcription, or protein synthesis under *any* condition, or *any* pH, temperature, composition of the substrate and presence/absence of an inducer condition; or lactic acid bacteria that are capable of increasing cell size without mitosis as encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1 (claims 9-11, dependent therefrom), 2-8, 12-17, and 23-27 are so broad as to encompass a method of modifying *any* substrate material or a method of manufacturing *any* food or feed product using *any* modified lactic acid bacterium as encompassed by the claims. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of modified and mutated lactic acid bacteria, substrates, compounds, food and feed products,

and starting materials broadly encompassed by the claims. Since the encoding polynucleotides and modifications thereof of a lactic acid bacterium determines its functional properties, predictability of which modifications can be tolerated in a lactic acid bacterium and obtain the desired biological activity requires a knowledge of and guidance with regard to which modifications, if any, the organism is tolerant of and detailed knowledge of the ways in which the modifications relate to the function of the bacterium. However, in this case the disclosure is limited to a method of acidifying milk by: a) propagating a culture of purine or thymidine auxotrophic lactic acid bacterium capable of acidifying milk in a medium containing purines or thymidine, respectively; and b) adding the culture to milk under conditions that allow acidification of the milk by the bacterium, whereby if the milk is contaminated with bacteriophage, the bacterium maintain the ability to acidify the milk, and optionally wherein the auxotrophic lactic acid bacteria overexpress Escherichia coli F1-ATPase for increased carbon flux through the glycolytic pathway.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple modifications, as encompassed by the instant claims, and the modifications to a lactic acid bacterium that can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to one modification to diminish with each further and additional modification to a lactic acid bacterium.

The specification does not support the broad scope of the claims which encompass a method of modifying *any* substrate material or a method of manufacturing *any* food or feed product using *any* modified lactic acid bacterium as encompassed by the claims because the specification does not establish: (A) *all* modifications or mutations that render a lactic acid strain auxotrophic to a specific compound required for replication in combination with a given substrate that lacks said compound, to disrupt DNA replication, RNA transcription, or protein synthesis of said auxotrophic lactic acid bacterium while maintaining the ability to metabolically act on a substrate and result in resistance to lysis by bacteriophage; (B) *all* components enhancing the viability of bacteria during storage; (C) compatible substrates that contain *any* compound that inhibits DNA replication, RNA transcription, or protein

synthesis while allowing the bacterium to metabolically act on said substrates and maintaining resistance to lysis by bacteriophage; (D) *all* modifications to a lactic acid bacterium that enhance *any* metabolic pathway or *any* pathway of claim 13 or enhance ATPase activity; (E) *any* condition(s) of claim 16 under which a lactic acid bacterium does not perform DNA replication, RNA transcription, or protein synthesis while maintaining the ability to metabolically act on a substrate and maintain resistance to lysis by bacteriophage; (F) *any* modification of a lactic acid bacterium that results in increasing the size of cells without mitosis; and (G) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a method of modifying *any* substrate material or a method of manufacturing *any* food or feed product using *any* modified lactic acid bacterium as encompassed by the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re* Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re* Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

14. Claims 4 and 5 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 4 and 5 are drawn to an invention that appears to employ novel bacteria. Since the bacteria is essential to the claimed invention, it must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The enablement requirement of 35 U.S.C. § 112, first paragraph, may be satisfied by a deposit of the bacteria. The specification does not disclose a repeatable process to obtain the bacteria and it is not apparent if the bacteria is readily available to the public. Accordingly, it is deemed that a deposit of this bacteria should have been made in accordance with 37 CFR 1.801-1.809.

It is noted that applicants have deposited the bacteria but there is no indication in the specification as to public availability. If the deposit was made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the specific strain has been deposited under the Budapest Treaty and that the strain will be irrevocably and without restriction or condition released to the public upon the issuance of the patent, would satisfy the deposit requirement made herein.

If the deposit has not been made under the Budapest treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, applicants may provide assurance or compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

1. during the pendency of this application , access to the invention will be afforded to the Commissioner upon request;

2. all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

3. the deposit will be maintained in a public repository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer; and

4. the deposit will be replaced if it should ever become inviable.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 1-4, 6-10, 15-17, 24-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dickely (US Patent 5,691,185) in view of Daly (Antonie van Leeuwenhoek 70:90-110, 1996) and Doskocil

(Biochem et Biophys Acta 145:780-791, 1967). Claims 1, 24, 26, and 27 are drawn to methods of modifying a substrate material or food or feed product using a bacterial culture that is not capable of DNA replication, RNA transcription, or protein synthesis and is metabolically active in the substrate material or food or feed product starting material and is not susceptible to attack by bacteriophage as encompassed by claims 1, 24, 26, and 27. Claims 2, 7, 8, and 25 further limit the substrate material or food product starting material. Claims 3, 4, 6, 9-10, 15-17 further limit the bacterial strain or culture.

Dickely teaches purine auxotrophic mutants (Pur-) of L. lactis that require sufficient amounts of purine nucleotides for replication (column 11) and methods of isolating such mutants (column 25). Dickely teaches that milk is a medium that contains insufficient amounts of purine or pyrimidine nucleotides to support the growth of purine or pyrimidine auxotrophs of lactic acid bacteria (columns 11 and 30). Dickely does not teach the use of Pur- mutant L. lactis for fermentation of a substrate material, a substrate material containing a compound that inhibits DNA replication, RNA transcription, or protein synthesis, or a food or feed product.

Daly teaches lactic acid bacteria, including the genus Lactococcus, is essential for the fermentation of a variety of food products such as milk (page 99). Daly teaches that one of the factors that contribute to poor Lactococcus starter culture performance is attack by lytic phage and is very difficult to overcome. Daly teaches that methods of phage resistance have been developed, however, novel mechanisms of phage resistance are required for a strain of phage-resistant Lactococcus bacteria (pages 99 and 107).

Doskocil teaches that 5-azacytidine, a cytidine analog, strongly inhibits the production of viable phage particles (page 780, summary) and teaches the mechanism of inhibition of phage production by 5-azacytidine is the inhibition of DNA synthesis (page 789), while protein and RNA synthesis remain largely unaffected (pages 780 and 790).

Also, one of ordinary skill in the art would have recognized that methods of fermenting milk using L. lactis are well known in the art, that Pur- mutants of L. lactis are unable to undergo mitosis in a medium lacking purine nucleotides because of the inability to synthesize DNA due to the disruption of

purine metabolism, and Pur- mutants of L. lactis that remain metabolically active necessarily increase in size.

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Daly, Doskocil, and Dickely to use the Pur- mutants of Dickely for growth of a starter culture of the Pur- mutants in a growth medium supplemented with purines, removal of the starter culture cells from the growth medium, and fermenation of milk using the L. lactis Pur- mutants and optionally to include 5-azacytidine in order to prevent bacterial lysis by phage. One would have been motivated to ferment milk using the Pur- L. lactis of Dickely and optionally including 5-azacytidine because L. lactis Pur- mutants would be unable to synthesize DNA as milk provides insufficient purines to support growth of the L. lactis Pur- mutants, thereby preventing lysis by phage. One would have a reasonable expectation of success for using the Pur- mutants of Dickely for growth of the Pur- mutants in a growth medium supplemented with purine nucleotides, removal of the cells from the growth medium, and fermenation of milk using the Pur- L. lactis mutants and optionally to include 5-azacytidine in order to prevent bacterial lysis by phage because of the results of Daly, Doskocil, and Dickely . Therefore, claims 1-4, 6-10, 15-17, and 24-27, drawn to methods of modifying a substrate material or food or feed product using a bacterial culture that is not capable of DNA replication, RNA transcription, or protein synthesis and is metabolically active in the substrate material or food or feed product starting material and is not susceptible to attack by bacteriophage would have been obvious to one of ordinary skill in the art.

It is noted that the examiner has applied the common knowledge of methods of fermenting milk using L. lactis, Pur- mutants of L. lactis being unable to undergo mitosis in a medium lacking purine nucleotides because of the inability to synthesize DNA due to the disruption of purine metabolism, and Pur- mutants of L. lactis that remain metabolically active necessarily increasing in size as all cells must inherently increase in size following mitosis or they would cease to exist. The cited common knowledge is capable of instant and unquestionable demonstration as being well known in the art. The examiner should not be obliged to spend time to produce documentary proof (see *In re* Malcolm, 129 F.2d 529, 54 USPQ 235 (CCPA 1942)). If applicants should challenge a factual assertion presented by the examiner as

not properly based upon common knowledge, applicants should specifically point out the supposed errors in the examiner's Office action, including stating why the noticed fact is not considered to be common knowledge or well-known in the art. See MPEP 2144.03 and 37 CFR 1.111(b).

16. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Dickely in view of Daly and Doskocil and as applied to claims 1-4, 6-10, 15-17, 24-27 and further in view of Ross (Appl Environ Microbiol 56:2164-2169, 1990). Claim 5 is drawn to a method of modifying a substrate material or food or feed product using an L. lactis thyA mutant.

Dickely, Daly, and Doskocil disclose the teachings as described above. The combined references of Dickely, Daly, and Doskocil do not combine to teach a method of practicing the claimed methods using a L. lactis thyA mutant.

Ross teaches thymidylate synthase (TS) plays a key role in DNA synthesis by catalyzing the conversion of dUMP to dTMP (page 2164). Ross teaches thyA- mutants, i.e., cells with a disrupted thymidylate synthase gene, require thymine or thymidine for DNA synthesis and growth and die in the absence of thymine or thymidine (page 2164). Ross teaches a method for identifying thyA- bacterial mutants (page 2164). Ross teaches Lactococcus lactis is used for the manufacture of cheese (page 2164).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Daly, Doskocil, Dickely, and Ross to use L. lactis thyA mutants for growth of a thyA mutant starter culture in a growth medium supplemented with thymidine, removal of the cells from the growth medium, and fermenation of milk using a L. lactis thyA mutant in order to prevent bacterial lysis by phage. One would have been motivated to ferment milk using a L. lactis thyA mutant because a L. lactis thyA mutant would be unable to synthesize DNA as milk provides insufficient pyrimindines to support growth of an L. lactis thyA mutant, thereby preventing lysis by phage. One would have a reasonable expectation of success for using L. lactis thyA mutants for growth of a thyA mutant in a growth medium supplemented with thymidine, removal of the cells from the growth medium, and fermenation of milk using a L. lactis thyA mutant in order to prevent bacterial lysis by phage because of the results of Daly, Doskocil, Dickely,

and Ross. Therefore, claim 5, drawn to a method of modifying a substrate material or food or feed product using an L. lactis thyA mutant would have been obvious to one of ordinary skill in the art.

17. Claims 12-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dickely in view of Daly and Doskocil and as applied to claims 1-4, 6-10, 15, 16, 24-27 and further in view of Snoep (WO 98/10089, 1998). Claims 12-14 are drawn to a method of modifying a substrate material using a bacterial culture that is not capable of DNA replication, RNA transcription, or protein synthesis and is metabolically active in the substrate material and is not susceptible to attack by bacteriophage, wherein the strain is enhanced in at least one metabolic pathway, glycolytic flux, flux through the pentose phosphate pathway, or ATPase activity.

Dickely, Daly, and Doskocil disclose the teachings as described above. The combined references of Dickely, Daly, and Doskocil do not combine to teach a method of practicing the claimed methods using an L. lactis Pur- mutant strain that is enhanced in at least one metabolic pathway, glycolytic flux, flux through the pentose phosphate pathway, or ATPase activity.

Snoep teaches that overexpression of bacterial F1-ATPase subunit of H^+-ATPase increases carbon flow through the glyclytic pathway by increasing the pool of available ADP (page 2), thereby increasing the production of lactic acid, which is important for bacteria involved in acidification and flavoring of dairy products (page 1). Snoep teaches overexpression of bacterial F1-ATPase would be especially useful for bacteria used in the dairy industry such as Lactococcus lactis (page 5). Snoep teaches the nucleic acid sequences of bacterial F1-ATPases and the expression of bacterial F1-ATPases in L. lactis (pages 21-26).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Daly, Doskocil, Dickely, and Snoep to use the Pur- mutants of Dickely overexpressing the F1-ATPase of Snoep for fermenation of milk. One would have been motivated to ferment milk using the Pur- L. lactis of Dickely overexpressing the F1-ATPase of Snoep in order to increase the production of lactic acid for a more rapid fermentation of milk. One would have a reasonable expectation of success for using the Pur- mutants of Dickely overexpressing the F1-ATPase of Snoep because of the results of Daly, Doskocil, Dickely, and Snoep. Therefore, claims 12-14, drawn to a method of modifying a substrate material using

a bacterial culture that is not capable of DNA replication, RNA transcription, or protein synthesis and is metabolically active in the substrate material or food or feed product starting material and is not susceptible to attack by bacteriophage, wherein the strain is enhanced in at least one metabolic pathway, glycolytic flux, flux through the pentose phosphate pathway, or ATPase activity would have been obvious to one of ordinary skill in the art.

18. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Dickely in view of Daly, Doskocil as applied to claims 1-4, 6-10, 15-17, and 24-27 above and further in view of Barach (US Patent 4,294,930). Claim 11 is drawn to a method of modifying a substrate material using a bacterial culture that is not capable of DNA replication, RNA transcription, or protein synthesis and is metabolically active in the substrate material, wherein the strain is added to the substrate material at a concentration of 10^5 to 10^9 CFU per mL or g of material.

Dickely, Daly, and Doskocil disclose the teachings as described above. The combined references of Dickely, Daly, and Doskocil do not combine to teach a method of practicing the claimed methods using a bacterial strain added to the substrate material at a concentration of 10^5 to 10^9 colony forming units (CFU) per milliliter or gram of the substrate material.

Barach teaches to facilitate handling and uniformity of a starter culture for milk fermentation, an effective microbial cell population is usually greater than about 10^8 CFU/mL (column 1).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Daly, Doskocil, Dickely, and Barach to use the Pur- mutants of Dickely for fermenation of milk using a starter culture concentration of 10^8 CFU/mL. One would have been motivated to ferment milk using a starter culture concentration of 10^8 CFU/mL of the Pur- L. lactis of Dickely in order to facilitate handling and uniformity of a starter culture as taught by Barach. One would have a reasonable expectation of success for using a starter culture of the Pur- mutants of Dickely at a concentration of 10^8 CFU/mL for the fermentation of milk because of the results of Daly, Doskocil, Dickely, and Barach. Therefore, claim 11, drawn to a method of modifying a substrate material using a bacterial culture that is not capable of DNA replication, RNA transcription, or protein synthesis and is metabolically active in the substrate material,

wherein the strain is added to the substrate material at a concentration of 10^5 to 10^9 CFU per mL or g of material would have been obvious to one of ordinary skill in the art.

Conclusion

19. All claims are rejected

20. No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Friday from 7:30 am to 2:00 pm and from 3:30 pm to 5:30 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for this Group is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

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